REMARKS

Claim 12 has been amended.

Examination and reconsideration of the application as amended is requested.

Applicants respectfully request entry of this Amendment After Final Rejection. The amendments to the claims raise no new issues that would require further consideration, no additional claims are presented, and no issues of new matter are raised as basis is provided in the specification for each new limitation.

§ 112 Rejections

Claim 12 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards (or Applicants regard) as the invention. The above amendment corrects this deficiency, and Applicant respectfully requests withdrawal of this rejection.

§ 103 Rejections

Claims 1-26 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Tomai et al. (WO 98/17279) and Gerster et al. (U.S. Pat. 6,110,929) in view of Bitterman-Deutsch et al. (HAREFUAH, 1990; 119(5-6);137-139), Mosbech et al. (Ugeskrift for Laeger, 1991;153(44):3067-3071), Binder (Medical Toxicology and Adverse Drug Experience, 1989;4(3):163-173), and Auerbach et al. (Journal of Emergency Medicine, 1987;5(6):487-491).

The eosinophil inhibition taught in Tomai is not relevant the necrotic arachnidism associated with dermal lesions caused by venom induced immune dysregulation. The term polymorphonuclear leukocyte describes three functionally distinct cell types, distinguished for example by staining characteristics in Wright-Giemsa blood film preparations. These are neutrophils, eosinophils, and basophils. Of these three, only neutrophils are relevant to nectrotic arachnidism. Since eosinophils are not relevant, knowledge that the compounds disclosed in Tomai and Gerster inhibit eosinophils would not motivation one skilled in the art to use this compounds to treat venom induced immune dysregulation. Furthermore, the compounds of Tomai and Gerster are not known to inhibit or interfere with the functional activity of neutrophils. For example, imiquimod, one of the compounds taught in Tomai, upregulates IL-8, which is a potent chemattractant for polymorphonuclear leukocytes. This would lead one skilled in the art to expect neutrophils to be attracted to the site where the compounds of Tomai and Gerster are applied.

For these reasons, the Bitterman reference does not provide one skilled in the art any motivation to use the compounds of Tomai and Gerster for treatment of venom induced immune dysregulation. Dapsone, which inhibits IL-8 production and reduces neutrophls, and the compounds of Tomai and Gerster have completely different mechanisms of action.

Necrotic arachnidism associated with venom induced dysregulation is not known to those skilled in the art to involve allergic, IgE or Th2 mediated immune responses. Thus, the Mosbech, Binder, and Auerbach references provide no motivation for one skilled in the art to use the compounds of Tomai and Gerster for treatment of venom induced immune dysregulation.

Applicants point out that their results are not only unexpected and unobvious, but also of statistical and practical significance. The results reported in the specification show that in the first group of 12 patients, managed using conventional therapy, 7 patients progressed to tissue necrosis. The next 7 cases treated with imiquimod resulted on 0 cases of tissue necrosis. The probability of this observation being due to chance alone is less than or equal to 1.7% using a Fisher's Exact Test procedure (P less than or equal to 0.017). Statistical significance is accepted at any P less than or equal to 0.05. The practical significance is clearly of great importance to patients suffering from these ailments.

Applicants have addressed each of the issues raised by the Examiner, and respectfully request withdrawal of the rejection of claims 1-26 under 35 U.S.C. § 103(a).

In view of the above, it is submitted that the application is in condition for allowance. Reconsideration of the application is requested. Allowance of claims 1-26, as amended, at an early date is solicited.

Respectfully submitted,

12 NOVEMBER 2002 By: Dean A. Ersfeld

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Version With Markings to Show Changes Made

12. The method of claim 1 wherein the source of [envenomation]the venom induced immune dysregulation is a marine animal.